The Examiner is respectfully requested to reconsider the rejections in the Office Action based on Applicants' amendments, on the comments below and on the aforementioned Rule 131 Declaration of James A. S. Nightingale.

Claims 1, 4, 15, 17, 22, 23, 26, 28-38, 49-51 and 53-56 are currently pending.

The rejections and Applicants' traversal

Claims 1, 4, 15, 17, 22, 23, 26, 28-38, 49-51 and 53-56 were rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement, the Examiner having contended that the claims contain new matter. The Examiner specifically stated that paragraphs [0020] and [0056] indicate that all the compositions have residual solvent, and that excluding residual solvent from the composition by amendment introduces compositions that are new to the instant invention.

Applicants respectfully disagree.

Paragraphs [0020] and [0056] do not mandate the presence of solvent in compositions according to the invention. Paragraph [0020] states that the amount of HPMCAS and drug in the dispersion should be at least 75% by weight, "...not counting any residual solvent...". That simply amounts to a statement that residual solvent, if there is any, should not be included when calculating the wt. % of individual constituents in the dispersion. Paragraph [0056] states a preferred embodiment, namely that the weight of residual solvent should preferably be less than 10 wt %, preferably less than 2 wt %. Neither paragraph is or contains a declaration that residual solvent must be present.

Applicants have simply chosen not to use the feature of residual solvent to distinguish over prior art. Applicants also note that the claims as originally filed did not require the presence of residual solvent, that limitation having been added by amendment in Applicants' response to the Office Action mailed on July 13, 2004. Hence compositions not explicitly containing a feature relating to residual solvent are not "new to the instant invention".

Reconsideration and withdrawal of the rejection is accordingly respectfully requested.

Claims 1, 4, 15, 17, 22, 23, and 53-56 stand rejected under 35 USC 103(a) over Kigoshi et al., US 6,254,889 (Kigoshi).

The rejection is obviated by the submission herewith of the Rule 131 Declaration of James A. S. Nightingale. The Nightingale declaration, together with the laboratory

notebook pages appended thereto, establishes completion of Applicants' invention prior to February 13, 1997, the PCT publication date for Kigoshi and the earliest date that Kigoshi would be available as a reference in the U. S. under 35 USC 103(a). Thus, Kigoshi has been removed as a reference, and it is accordingly respectfully requested that the §103(a) rejection over Kigoshi be withdrawn.

Claims 1, 4, 15, 17, 22, 49-51 and 53-56 continue to be rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993). The Examiner, *inter alia*, described the difference between Applicants' invention and Yamaguchi as follows:

> The difference between Yamaguchi and the instant claims after the current amendment is that Yamaguchi discloses ratios of 2:1, 5:1, 10:1 and 20:1 for the drug to polymer while the instant claims disclose a ratio of 1:0.4 to 1:20. The claimed ratio goes through a point of 1:1 at least, and from the claimed range, it appears any of those ratios of drug to polymer would work in the claimed invention. There is also no demonstration in applicant's specification that any of those specific ratios provide unexpected results to the claimed composition. Yamaguchi does not disclose any amount of residual solvent that may be present or not present after the spray drying process. While the ratio of the drug to polymer in Yamaguchi is increased upward from 2:1, 5:1, 10:1 and 20:1, it is examiner's position a ratio of 2:1 is not drastically very far different from the claimed ratio where one of the points is 1:1. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition of solid amorphous dispersion according to Yamaguchi where the drug to polymer is in a ratio of 2:1. One having ordinary skill in the art would have been motivated to use various ratios of the drug to polymer, including 1:1 and 2:1 and 1:2 with the expectation of increasing the solubility and bioavailability of MAT, which is an objective of Yamaguchi. In the absence of a factual showing, specifically indicating that the claimed spray dried dispersion having a drug:polymer ratio of 1:0.4 to 1:20 provides unexpected results over the spray dried dispersion of the prior art having a drug:polymer ratio of 2:1, the claimed composition is not inventive over the prior art.

As a preliminary matter, Applicants note that the Examiner spent a considerable portion of her argument contending that obviousness would lie because of the 2:1 to 20:1 ratios taught by Yamaguchi for MAT:CMEC, contending that "[w]hile the ratio of the drug to polymer in Yamaguchi is increased upward from 2:1, 5:1, 10:1 and 20:1, it is examiner's position a ratio of 2:1 is not drastically very far different from the claimed ratio where one of the points is 1:1." Applicants point out that the ratios noted by the Examiner are for MAT and CMEC, not for MAT and HPMCAS. Only a single

MAT/HPMCAS composition was disclosed in Yamaguchi, and the MAT/HPMCAS ratio (10:1) for that composition is well outside the range required by Applicants.

The Examiner appeared to be treating the ratios Yamaguchi discloses for MAT:CMEC as though they apply to MAT:HPMCAS. Applicants' contend that they clearly do not. The Examiner cited, *inter alia*, the statement in Yamaguchi that "Preparation was similarly carried out using AQOAT® or EC as the carrier". Yamaguchi, Page 2, last line. Applicants again submit, for the reasons set forth in their previous response which are hereby incorporated by reference, that that statement in Yamaguchi would clearly be understood as meaning that the process used to make Yamaguchi's MAT:polymer compositions were the same whether CMEC, EC, or HPMCAS was used as the polymer. That statement does not indicate that the same ratios were used for each MAT:polymer combination. To see which ratios were prepared for each MAT:polymer combination, one would consult the Yamaguchi text to determine the specific ratios disclosed. They would see that Yamaguchi explicitly discloses only a single MAT:HPMCAS composition having a 10:1 ratio. The ratios within the range of 2:1 to 20:1 disclosed in Yamaguchi were explicitly disclosed only for MAT:CMEC. In addition to the reasons previously presented in support of this contention, Applicants submit it is illogical to contend that Yamaguchi made MAT:HPMCAS compositions having the same ratios as the ones explicitly disclosed for MAT:CMEC and then never disclosed anything further about them. To repeat, the ordinarily skilled art worker would look for further guidance as to which MAT:HPMCAS compositions were actually prepared and find none beyond the single 10:1 composition explicitly disclosed for MAT:HPMCAS.

The rejection is further traversed for the reasons presented below, especially that Yamaguchi teaches away from the invention. One of ordinary skill in the art would not find it obvious to vary the ratios in the manner alleged by the Examiner because the results Yamaguchi achieved with MAT and CMEC would discourage one from applying Yamaguchi's MAT:CMEC ratios to MAT:HPMCAS.

Applicants' position is that a patentable distinction over Yamaguchi is the drug:HPMCAS polymer range required by Applicants, that range being 1:0.4 to 1:20. As previously noted, the lone MAT:HPMCAS composition disclosed in Yamaguchi has a ratio of 10:1 (see Yamaguchi's Figure 2).

The MAT:CMEC values disclosed by Yamaguchi are 2:1, 5:1, 10:1, and 20:1, as noted by the Examiner, i.e., the MAT:CMEC ratios span a range of 2:1 to 20:1.

Yamaguchi, page 2, item 2. The issue is whether it would be obvious to make drug:HPMCAS compositions (including MAT:HPMCAS compositions) having a greater amount of HPMCAS than that for the lone MAT:HPMCAS composition disclosed in Yamaguchi having a MAT:HPMCAS ratio of 10:1.

Based on the results Yamaguchi disclosed for his MAT:CMEC ratios, one of ordinary skill in the art would not find it obvious to make MAT:HPMCAS compositions having an amount of polymer greater than that used in the single 10:1 MAT:HPMCAS composition Yamaguchi actually disclosed. That is because Yamaguchi's results with MAT and CMEC teach that the more polymer one includes in a drug:polymer composition, the lower the concentration enhancement that is achieved. The concentration enhancements achieved by Yamaguchi for his MAT:CMEC compositions are summarized in his Figure 4 as annotated by Applicants in their previous response, and which Applicants reproduce below for convenience.

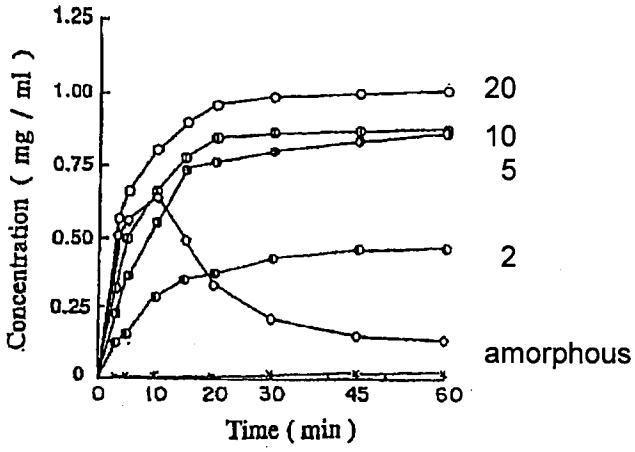

Fig. 4. Dissolution Patterns of MAT from MAT-CMEC Solid Dispersion in Acidic Solution (pH 4.0) at 37.0℃
Mixing ratio of MAT and CMEC : ◐, 10/5 ; ◑, 10/2; ⓘ, 10/1 ; ○, 10/0.5; ◇, amorphous MAT without CMEC; ×, crystalline MAT.

Applicants' results, as detailed in the declaration of Dwayne T. Friesen previously submitted and in contrast with Yamaguchi, demonstrate that superior concentration enhancement is achieved by using relatively greater amounts of HPMCAS, not greater amounts of drug as taught by Yamaguchi for MAT:CMEC. Contrary to the Examiner's position that Applicants have not shown unexpected results, Applicants have indeed

shown unexpected and surprising results with HPMCAS (greater amounts of HPMCAS result in greater concentration enhancement) relative to Yamaguchi (greater amounts of CMEC result in less concentration enhancement). Yamaguchi clearly teaches the opposite result to Applicants, and for that reason one of ordinary skill in the art would not find it obvious to make MAT:HPMCAS compositions (or any other drug:HPMCAS compositions, for that matter) having a drug:HPMCAS ratio lower than 10:1, i.e., containing an increased amount of HPMCAS relative to drug. Yamaguchi, considering his MAT:CMEC results, would discourage increasing the relative amount of HPMCAS in MAT:HPMCAS dispersions.

It is accordingly respectfully requested that the Examiner reconsider and withdraw the rejection. Yamaguchi clearly teaches away from the subject matter claimed by Applicants, and that is strong evidence of unobviousness. W. L. Gore & Assocs., Inc. v. Garlock, Inc. , 721 F.2d 1540, 1552, 220 U. S. P. Q. 303, 312 (Fed. Cir. 1983), cert. denied, 469 U. S. 851 (1984).

The claims continue to be rejected under 35 USC 103(a) as unpatentable over Miyajima et al. (US 4,983,593). Applicants traverse the rejection for the reasons given below. The Examiner stated, *inter alia*, that:

> The Remington reference does state that spray drying leads to "crystals and/or amorphous solids depending on the rate and conditions of solvent removal." Thus, the Remington reference further supports the fact that spray drying leads to amorphous products. It is respectfully noted that the invention is directed to a composition and a composition that is formed by spray drying. Applicants appear to imply that the spray dried product of Miyajima may or may not be amorphous, and if this is the case, it may also raise the question whether applicants product is amorphous since the claimed product is formed/prepared by spray drying. Although, applicants argue that Miyajima mentions spray drying only once in the disclosure and as such cannot be relied upon for spray drying, it is the Examiner's position that there is a disclosure of spray drying in Miyajima. The claims are composition claims. Also, the recitation of spray-dried particles solidifying in less than 5 seconds is an inherent characteristic of the spray drying process. However, both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Miyajima solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by spray drying as does the claimed invention differs in any way from the claimed solid dispersion.

The Examiner further stated that the Declaration of Scott B. McCray, submitted with Applicants' previous response, "...is not commensurate with the claims and even with the disclosure of Miyajima as it relates to spray drying."

Applicants traverse on the basis previously submitted, and present additional reasoning as follows:

1. The instant claims require that the dispersion consist essentially of the drug and HPMCAS, and that the drug be molecularly dispersed and amorphous in the dispersion. Miyajima never described or exemplified any spray dried dispersion, or how to achieve a dispersion in which the drug is molecularly dispersed and amorphous.

2. Applicants previously submitted the Remington article demonstrating that materials that are spray dried can contain particles consisting of crystals and/or amorphous solids, depending on the **rate** and **conditions** of solvent removal. That is, spray drying does not necessarily and/or inherently produce amorphous drug regardless of the conditions employed.

3. The Examiner's comment (Office Action, page 10, lines 3-5) that "...since Miyajima discloses spray drying, even if it is just once, and since the instant invention prepares amorphous dispersions by spray drying, then Miyajima' product would be amorphous" is legally tenable only if solid amorphous spray dried dispersions are inherently (i.e., necessarily and unavoidably) produced by spray drying. Remington shows that solid amorphous dispersions are not inherently produced by spray drying, however. Indeed that was Applicants' reason for submitting Remington. With no basis for inherency, the Examiner's contention that "...[t]hus, the Remington reference further supports the fact that spray drying leads to amorphous products" is legally incorrect.

4. Applicants also submitted the declaration of Scott B. McCray which demonstrated that a granulation made following the method outlined in example 6 of Miyajima does not form a homogeneous solid amorphous dispersion, as confirmed by differential scanning calorimetry (DSC) and x-ray diffraction (PXRD). In fact, about two-thirds of the drug, nicardipine hydrochloride, was crystalline. The McCray declaration supports that dispersions produced by vacuum drying, disclosed in Myajima without distinction from spray drying, are not dispersions in which the drug is molecularly dispersed and amorphous. The only disclosure of spray drying in Miyajima is the one-time mention of the phrase "spray drying" per se, in passing and as part of a list of solvent removal processes. But, because amorphous drug is not inherently produced by spray drying (see Remington), mentioning the phrase is not a disclosure or teaching of

how to make a dispersion consisting essentially of drug and HPMCAS in which the drug is molecularly dispersed and amorphous.

5. The Examiner's comment (Office Action, page 12) to the effect that the McCray "declaration is not commensurate with the claims and even with the disclosure of Miyajima as it relates to spray drying" is inapposite. The McCray declaration presented evidence (using nicardipine hydrochloride since NZ-105, efonidipine hydrochloride, was not available) demonstrating that Miyajima did not, by a vacuum drying method, produce a dispersion consisting essentially of drug and HPMCAS in which the drug was molecularly dispersed and amorphous. The issue probed by the declaration was whether Miyajima had made an amorphous dispersion by vacuum drying. Because the issue related to producing amorphous drug by vacuum drying as presented in Miyajima, it was not intended to probe "...spray drying as disclosed in Miyajima". Indeed, that would not be possible since Miyajima presented no actual example or description of spray drying with which Applicants could make any comparison.

6. The declaration therefore presented evidence that Miyajima did not produce, by a vacuum drying method as outlined in his example 6, a dispersion in which the drug was molecularly dispersed and amorphous. Because Miyajima made no distinction between vacuum drying and spray drying under conditions that would produce an amorphous dispersion, this highlighted the fact that Miyajima did not appreciate the advantage of a dispersion in which the drug was molecularly dispersed and amorphous. So far as the Examiner's comments in regard to the scope of the McCray declaration vis a vis Miyajima are concerned, Applicants made their comparison with the only working example in Miyajima (as opposed to a comparative example) that used vacuum drying.

7. Thus, however one chooses to characterize the composition Miyajima described in his example 6, as evidenced by Applicants using nicardipine hydrochloride and HPMCAS, it is not a dispersion consisting essentially of drug and HPMCAS in which the drug is molecularly dispersed and amorphous. When Applicants conducted the method outlined in the example using HPMCAS and nicardipine hydrochloride, the product contained a significant amount of crystalline drug.

8. In summary of the points made above, (1) spray drying does not inherently produce dispersions in which the drug is molecularly dispersed and amorphous (see Remington) (2) Miyajima never exemplified an actual spray dried dispersion that could be tested or compared and (3) Miyajima did not otherwise appreciate and/or teach how

to make a dispersion in which the drug is molecularly dispersed and amorphous. Rhetorically, how can Applicants' invention be obvious over a reference that does not teach or exemplify how to make an amorphous dispersion and that is silent about such dispersions otherwise? Clearly, Miyajima did not appreciate the importance of the drug being molecularly dispersed and amorphous.

The Examiner's point (Office Action, page 11, first 3 lines) that "[a]pplicants appear to imply that the spray dried product of Miyajima may or may not be amorphous, and if this is the case, it may also raise the question whether applicants product is amorphous since the claimed product is formed/prepared by spray drying" is acknowledged and traversed. Applicants have extensively detailed and exemplified processes for making a dispersion in which the drug is molecularly dispersed and amorphous. Such dispersions constitute the focus of Applicants invention and the focus of their description and enablement. Miyajima, by contrast, did not appreciate the importance of the drug being molecularly dispersed and amorphous and taught nothing about it.

Apart from the comments above relating to the McCray declaration, Applicants note that Miyajima made no distinction between dispersions produced by vacuum evaporation relative to dispersions in which the drug is molecularly dispersed and amorphous. Miyajima exemplified dispersions made using drying in vacuo, but disclosed nothing about the performance of his vacuum dried dispersions relative to dispersions according to the instant invention. Due, inter alia, to the fast solidification time and low residual solvent level used according to the present invention (see page 16, lines 6 to 8 and 13 to 26 of the description), dispersions are made by spray drying such that the drug is molecularly dispersed, which dispersions effect better concentration enhancement than the relatively non-homogeneous dispersions made by a vacuum evaporation method. In addition to the McCray declaration, Applicant also conclusively demonstrated this point in the examples of their description (see applicant's Example 24 and Comparative Example C9; Example 29 and C13 in the instant application). One of ordinary skill would thus not find applicant's solid amorphous dispersions obvious from Miyajima, especially considering that Miyajima does not distinguish spray drying from any other solvent removal process also disclosed therein.

In summary, and for all of the above reasons, Applicants contend that the mere mention of the phrase "spray drying" once in Miyajima does not teach or make obvious a dispersion in which the drug is molecularly dispersed and amorphous. Remington

clearly shows that spray drying does not necessarily produce amorphous drug. Miyajima contains no teaching as to how the skilled person would make a polymer/drug dispersion in which the drug is amorphous, or as to what factors might be important if one wanted to do so. Given the absence of any guidance in Miyajima, one of ordinary skill could just as easily make a spray dried material containing crystals, as confirmed in Remington, as make an amorphous dispersion, as disclosed in Applicants' specification and as required by Applicants' claims. Only the present application has provided such disclosure that details the requirements (see page 15, line 31 to page 16, line 26) and that enables making an amorphous dispersion, and those requirements are reflected in applicant's claims.

Withdrawal of the 103(a) rejection over Miyajima is accordingly respectfully requested.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited. The Commissioner is hereby authorized to charge any additional fees which may be required, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

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